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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 405/12, 401/12, 409/12, 471/04, 215/42, A61K 31/4706, 31/4375, A61P 25/00, 3/04

A1

(11) International Publication Number: **WO 00/47576**

(43) International Publication Date: 17 August 2000 (17.08.00)

(21) International Application Number: PCT/EP00/01148

(22) International Filing Date: 10 February 2000 (10.02.00)

(30) Priority Data:

9903288.0	12 February 1999 (12.02.99)	GB
9903287.2	12 February 1999 (12.02.99)	GB

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

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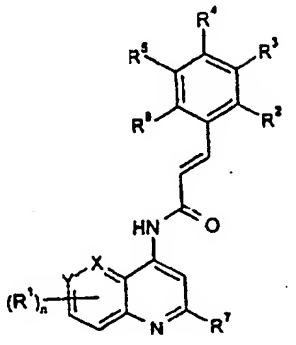
(54) Title: CINNAMIDE DERIVATIVES AS OREXIN-1 RECEPTORS ANTAGONISTS



(I)

(57) Abstract

A compound of formula (I): in which X and Y are CH, or one of X and Y is N and the other is CH; R^1 represents (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{1-6})alkoxy, any of which may be optionally substituted; halogen, R^8CO– or $NR^9R^{10}CO$–; R^2, R^3, R^4, R^5 and R^6 independently represent(C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxy or (C_{1-6})alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl(C_{1-6})alkyloxy, aryl(C_{1-6})alkyl, R^8CO–, R^8SO_2NH–, R^8SO_2O–, $R^8CON(R^{11})$–, NR^9R^{10}–, $NR^9R^{10}CO$–, –$COOR^9$, $R^{11}C(=NOR^8)$, heterocyclyl or heterocyclyl (C_{1-6})alkyl; or an adjacent pair of R^2, R^3, R^4, R^5 and R^6 together with the carbon atoms to which they are attached from an optionally substituted carbocyclic or heterocyclic ring; R^7 is hydrogen, (C_{1-6})alkyl (C_{1-6})alkenyl, (C_{1-6})alkoxy or (C_{1-6})alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano; NR^9R^{10}–, $NR^9R^{10}CO$– N_3, –$OCOR^9$ or $R^8CON(R^{11})$–; R^8 is (C_{1-6})alkyl, (C_{2-6})alkenyl, heterocyclyl, heterocyclyl (C_{1-6})alkyl, aryl or aryl(C_{1-6})alkyl, any of which may be optionally substituted; R^9 and R^{10} independently represent hydrogen, (C_{1-6})alkyl, (C_{2-6})alkenyl, heterocyclyl, heterocyclyl(C_{1-6})alkyl, aryl or aryl(C_{1-6})alkyl, any of which may be optionally substituted; R^{11} is hydrogen or (C_{1-6})alkyl, and when X and Y are both CH, n is 0, 1, 2, 3 or 4, and when X or Y is N, n is 0, 1, 2 or 3; or a pharmaceutically acceptable salt thereof. The use of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antogonist of a human orexin receptor is required.

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CINNAMIDE DERIVATIVES AS OREXIN-1 RECEPTORS ANTAGONISTS

This invention relates to cinnamide derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to,depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, *e.g.* HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain including irritable bowel

syndrome, migraine and angina; urinary bladder incontinence *e.g.* urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

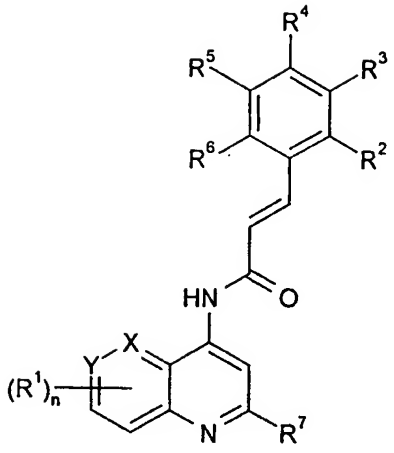
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulfonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitisers will be useful for many diabetics, however they do not have an anti-obesity effect.

Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

International Patent Applications PCT/GB98/02437 and PCT/EP99/03100 (published after the priority date of the present application) disclose various phenyl urea derivatives as orexin receptor agonists

The present invention provides cinnamide derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity including obesity observed in Type 2 (non-insulin-dependent) diabetes patients and/or sleep disorders.

According to the invention there is provided a compound of formula (I):



(I)

in which:

X and Y are CH, or one of X and Y is N and the other is CH;

R^1 represents (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{1-6})alkoxy, any of which may be optionally substituted; halogen, R^8CO- or $NR^9R^{10}CO$-;

R^2, R^3, R^4, R^5 and R^6 independently represent (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxy or (C_{1-6})alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl(C_{1-6})alkyloxy, aryl(C_{1-6})alkyl, R^8CO-, R^8SO_2NH-, R^8SO_2O-, $R^8CON(R^{11})$-, NR^9R^{10}-, $NR^9R^{10}CO$-, -$COOR^9$, $R^{11}C(=NOR^8)$, heterocyclyl or heterocyclyl(C_{1-6})alkyl;

or an adjacent pair of R^2, R^3, R^4, R^5 and R^6 together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

R^7 is hydrogen, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxy or (C_{1-6})alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, NR^9R^{10}-, $NR^9R^{10}CO$-, N_3, -$OCOR^9$ or $R^8CON(R^{11})$-;

R^8 is (C_{1-6})alkyl, (C_{2-6})alkenyl, heterocyclyl, heterocyclyl(C_{1-6})alkyl, aryl or aryl(C_{1-6})alkyl, any of which may be optionally substituted;

R^9 and R^{10} independently represent hydrogen, (C_{1-6})alkyl, (C_{2-6})alkenyl, heterocyclyl, heterocyclyl(C_{1-6})alkyl, aryl or aryl(C_{1-6})alkyl, any of which may be optionally substituted;

R^{11} is hydrogen or (C_{1-6})alkyl; and

when X and Y are both CH, n is 0, 1, 2, 3 or 4, and when X or Y is N, n is 0, 1, 2 or 3; or a pharmaceutically acceptable salt thereof.

Within the compounds of formula (I) two specific classes of compounds which may be mentioned are compounds of formula (IA) in which X and Y are CH, and compounds of formula (IB) in which one of X and Y is N and the other is CH.

A further group of compounds of formula (I) which may be mentioned are those in which R^2, R^3, R^4, R^5 and R^6 independently represent (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxy or (C_{1-6})alkylthio, any of which may be optionally substituted; hydrogen, halogen,

nitro, cyano, aryloxy, aryl(C_{1-6})alkyloxy, aryl(C_{1-6})alkyl, R^8CO-, R^8SO_2NH-, $R^8CON(R^{11})$-, NR^9R^{10}-, $NR^9R^{10}CO$-, -$COOR^9$, heterocyclyl or heterocyclyl(C_{1-6})alkyl;

or an adjacent pair of R^2, R^3, R^4, R^5 and R^6 together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

R^8 is (C_{1-6})alkyl or aryl; and

R^9 and R^{10} independently represent hydrogen, (C_{1-6})alkyl, aryl or aryl(C_{1-6})alkyl.

When either X or Y is CH, this does not preclude substitution of that carbon atom by an R^1 group.

When a halogen atom is present in the compound of formula (I) this may be fluorine, chlorine, bromine or iodine.

When one of X and Y is N, X is preferably N and Y is CH.

When either X or Y is N, n is preferably 0 or 1.

When X and Y are CH, n is preferably 1 or 2, also preferred is n is 0 or 1.

When n is 1, the group R^1 is preferably in the 6- or 8-position.

When both X and Y are CH and n is 2, the groups R^1 are preferably in the 6- and 8-positions.

R^1 is preferably halogen *e.g.* fluoro, or (C_{1-6})alkoxy *e.g.* methoxy. R^1 is most preferably fluoro.

When any one of R^1 to R^{11} comprise a (C_{1-6})alkyl group, whether alone or forming part of a larger group, *e.g.* alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, it preferably contains 1 to 4 carbon atoms and is most preferably methyl or ethyl.

When any one of R^1 to R^{10} comprise a (C_{2-6})alkenyl group, whether alone or forming part of a larger group, the alkenyl group may be straight chain, branched or cyclic, it preferably contains 2 to 4 carbon atoms and is most preferably allyl.

Suitable optional substituents for (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxy and (C_{1-6})alkylthio groups include one or more substituents selected from halogen *e.g.* fluoro, (C_{1-4})alkoxy *e.g.* methoxy, hydroxy, carboxy and (C_{1-6})alkyl esters thereof, amino, mono- or di-(C_{1-6})alkylamino and cyano.

When used herein the term "aryl", whether alone or forming part of a larger group, includes optionally substituted aryl groups such as phenyl and naphthyl, preferably phenyl. The aryl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Examples of suitable substituents for aryl groups include halogen, (C_{1-4})alkyl *e.g.* methyl, (C_{1-4})haloalkyl *e.g.* trifluoromethyl, (C_{1-4})alkoxy *e.g.* methoxy, (C_{1-4})alkoxy(C_{1-4})alkyl *e.g.* methoxymethyl, hydroxy, carboxy and (C_{1-6})alkyl esters thereof, amino, nitro, arylsulfonyl *e.g.* p-toluenesulfonyl, and C_{1-4} alkylsulfonyl *e.g.* methanesulfonyl.

When any one of R^2 to R^6 or R^8 to R^{10} represent heterocyclyl or heterocyclyl(C_{1-6})alkyl the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated or unsaturated, for example containing 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulfur; for example pyrrolidine, oxazole, morpholine, pyrimidine or phthalimide. A ring containing one or two nitrogen atoms is especially preferred. The

heterocyclyl group may contain up to 5, more preferably 1, 2 or 3 optional substituents. Examples of suitable substituents for heterocyclyl groups include halogen, (C_{1-4})alkyl *e.g.* methyl, (C_{1-4})haloalkyl *e.g.* trifluoromethyl, (C_{1-4})alkoxy *e.g.* methoxy, (C_{1-4})alkoxy(C_{1-4})alkyl *e.g.* methoxymethyl, hydroxy, carboxy, amino, nitro, arylsulfonyl *e.g.* p-toluenesulfonyl, and (C_{1-4})alkylsulfonyl *e.g.* methanesulfonyl.

When an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form a carbocyclic or heterocyclic ring this is preferably a 5- to 7-membered ring, which may be aromatic or non-aromatic. Heterocyclic rings preferably contain 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulfur; for example oxazole, imidazole, thiophene, pyran, dioxan, pyrrole or pyrrolidine. A ring containing one nitrogen atom or two oxygen atoms is preferred. A carbocyclic or heterocyclic ring formed by an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached may be optionally substituted on carbon or nitrogen by one or more substituents, *e.g.* up to 3 substituents. Examples of suitable substituents for the carbocyclic or heterocyclic ring include =O, (C_{1-4})alkyl *e.g.* methyl, aryl(C_{1-4})alkyl *e.g.* benzyl or 3-phenylpropyl, aryl *e.g.* phenyl, (C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl *e.g.* methoxymethyl, hydroxy, hydroxy(C_{1-4})alkyl *e.g.* hydroxyethyl, R^aCO_2-, R^aCO_2(C_{1-4})alkyl *e.g.* carboethoxypropyl, cyano, cyano(C_{1-4})alkyl *e.g.* 3-cyanopropyl, R^aR^bN and R^aR^bN(C_{1-4})alkyl; in which R^a and R^b are independently selected from hydrogen and (C_{1-4})alkyl.

A preferred group of compounds are those in which R^2 to R^6 independently represent hydrogen, halogen, (C_{1-6})alkoxy *e.g.* methoxy, (C_{1-6})alkylthio *e.g.* methylthio, or NR^9R^{10} wherein R^9 and R^{10} preferably represent (C_{1-6})alkyl *e.g.* dimethylamino, and at least one of R^2 to R^6 is other than hydrogen; or an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring, *e.g.* a 6- or 7-membered non-aromatic heterocyclic ring or a 5- or 6-membered aromatic heterocyclic ring.

A further preferred group of compounds are those in which R^7 is other than hydrogen.

A further preferred group of compounds are those in which R^5 or R^6 represent hydrogen.

A further preferred group of compounds are those in which R^4 and R^6 represent hydrogen.

A preferred group of compounds are those in which either R^3 and R^4, or R^3 and R^5 are other than hydrogen. A further preferred group of compounds are those in which either R^2 or R^2 and R^3 are other than hydrogen.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids *e.g.* hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids *e.g.* succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-

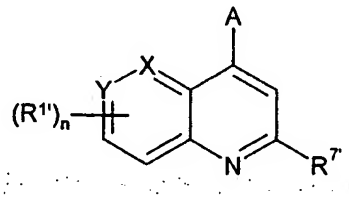
toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts *e.g.* oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

The invention extends to all isomeric forms including stereoisomers and geometric isomers of the compounds of formula (I) including enantiomers and mixtures thereof *e.g.* racemates. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

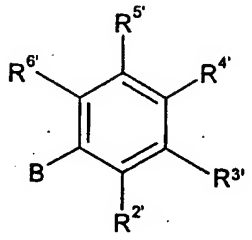
According to a further feature of the invention we provide a process for the preparation of the compounds of formula (I) or a salt thereof which comprises:

a) coupling a compound of formula (II):



(II)

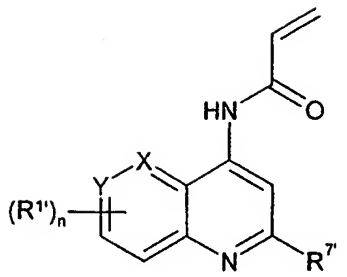
with a compound of formula (III):



(III)

where A and B are appropriate functional groups to form the –NHCOCH=CH- moiety when coupled; n, X and Y are as defined in formula (I); and $R^{1'}$ to $R^{7'}$ are R^1 to R^7 as defined in formula (I) or groups convertible thereto; or

b) coupling a compound of formula (IV):



(IV)

wherein n, X and Y are as defined in formula (I); and $R^{1'}$ and $R^{7'}$ are R^1 and R^7 as defined in formula (I) or groups convertible thereto; with a compound of formula (III) where B is a halogen or trifluoromethanesulfonate, in the presence of a palladium catalyst, a phosphine and a base; and

c) thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$ to $R^{7'}$ when other than R^1 to R^7 respectively to R^1 to R^7, and/or forming a pharmaceutically acceptable salt thereof.

Suitable examples of groups A and B are:

(i) A is $-NH_2$ and B is -CH=CH-COOH

(ii) A is $-NH_2$ and B is -CH=CH-COCl and

(iii) A is $-CO_2H$ and B is -CH=CH-COOH.

When A is $-NH_2$ and B is -CH=CH-COOH the reaction is generally effected in the presence of an agent such as O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and in the presence of a base such as di-isopropylethylamine at ambient or elevated temperature.

When A is $-NH_2$ and B is -CH=CHCOCl the reaction is generally effected in the presence of a reagent such as 4-dimethylaminopyridine at ambient or elevated temperature in a solvent such as dichloromethane or pyridine.

When A is $-CO_2H$ and B is -CH=CH-COOH the reaction is generally effected in the presence of a reagent such as diphenylphosphoryl azide and in the presence of a base such as triethylamine at ambient or elevated temperature as appropriate.

When B is halogen it is preferably bromo or iodo.

When a compound of formula (IV) is coupled with a compound of formula (III) a suitable base is triethylamine and the reaction is suitably carried out at room temperature or elevated temperature, preferably at an elevated temperature for example reflux.

Suitable palladium catalysts include palladium acetate.

A suitable phosphine is tri-o-tolylphosphine.

Suitable examples of compounds having groups $R^{1'}$ to $R^{7'}$ which are convertible to R^1 to R^7 respectively include compounds where one or more of $R^{2'}$ to $R^{6'}$ are OH or NH_2; and compounds where an adjacent pair of $R^{2'}$ to $R^{6'}$ together with the carbon atoms to which they are attached represent a fused pyrrole ring which is unsubstituted on nitrogen, where treatment with a base, *e.g.* sodium hydride, and reaction with an electrophile, *e.g.* methyl iodide, benzyl chloride or benzenesulfonyl chloride, affords the corresponding substituent on the pyrrole nitrogen.

Compounds of formula (II) where A is $-NH_2$ or CO_2H are known compounds or can be prepared analogously to known compounds.

Compounds of formula (III) where B is -CH=CH-COOH or -CH=CH-COCl are known compounds or can be prepared analogously to known compounds.

Compounds of formula (III) where B is halogen or trifluoromethanesulfonate are known compounds or can be prepared analogously to known compounds.

Compounds of formula (IV) are known compounds or can be prepared analogously to known compounds.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable salts thereof.

Novel intermediates of formula (II), (III) and (IV) are also part of this invention.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

As indicated above the compounds of formula (I) and their pharmaceutically acceptable salts, are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required especially feeding disorders, such as obesity and diabetes; prolactinoma; hypoprolactinemia, hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain, restless leg syndrome, heart and lung diseases, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; bulimia; and hypopituitarism.

The compounds of formula (I) and their pharmaceutically acceptable salts are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer

pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The present invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

For use in medicine, the compounds of the present invention are usually administered as a pharmaceutical composition. The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of formula (I) and their pharmaceutically acceptable salts, may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable salts, which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The dose of the compound of formula (I), or a pharmaceutically acceptable salt thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However as a general rule suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg; such unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of physiologically acceptable salts the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

Human orexin-A referred to above has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu
1 5 10 15
Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr
20 25 30
Leu-NH_2

Orexin-A can be employed in a process for screening for compounds (antagonists) which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on the surface thereof. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is employed to transfect cells to thereby express the receptor. The expressed receptor is then

contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional response.

One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor. Such a screening technique is described in WO 92/01810.

Another such screening technique involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes may then be contacted with a receptor ligand and a compound to be screened, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on the surface thereof. Such a method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand can be labelled, *e.g.* by radioactivity. The amount of labelled ligand bound to the receptors is measured, *e.g.* by measuring radioactivity of the receptors. If the compound binds to the receptor as determined by a reduction of labelled ligand which binds to the receptors, the binding of labelled ligand to the receptor is inhibited.

Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor. The ligand used in the screening method described below to determine the antagonist activity of compounds according to the invention is orexin-A which has the amino acid sequence shown above.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The following Descriptions **D1-D18** illustrate the preparation of intermediates to compounds of the present invention.

In the Examples ^{1}H NMR's were measured at 250MHz in d_6-DMSO unless otherwise stated. All hydrochloride salts unless otherwise stated were prepared by dissolving/suspending the free-base in methanol and treating with an excess of ethereal HCl (1M).

Description 1 (E)-Ethyl 3-[2-(furan-2-yl)phenylacrylate (D1)

A mixture of (E)-ethyl 2-bromophenylacrylate (4.54g), 2-furanylboronic acid (2.0g) and palladium-IV-*tetrakis*triphenylphosphine (0.60g) in benzene (50ml) containing ethanol (10ml) and saturated sodium hydrogen carbonate (10ml) was boiled for 16h. Solvent was removed to give a semi-solid which was extracted with dichloromethane. The

dichloromethane extracts were combined and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, petroleum ether:diethyl ether mixtures) to give the title compound (4.0g). $^{m}/_{z}$ (API^{+}): 243 (MH^{+}).

Description 2 (E)-3-[2-(Furan-2-yl)phenyl]acrylic acid (D2)

D1 (4.0g) in methanol/ sodium hydroxide (2M)(100ml/100ml) was stirred at 50°C for 1h. Solvent (100ml) was removed at reduced pressure, HCl (2M,120ml) added and the mixture extracted with ethyl acetate. The combined ethyl acetate extracts were evaporated to dryness and recrystallised from chloroform. The filtrate from the recrystallisation was evaporated to dryness and column chromatographed (silica gel, petroleum ether:diethyl ether mixtures as eluant) to give the title compound. ^{1}H NMR δ: 5.90 (1H, dd, J = 2+10Hz), 6.40 (1H, dd, J = 2+17Hz), 6.85 (1H, dd, J = 10+17Hz), 7.66 (1H, dt, J = 1+7Hz), 7.79 (1H, dt, J = 1+7Hz), 8.01 (1H, dd, J = 1+8Hz), 8.20 (1H, d, J = 5Hz), 8.38 (1H, d, J = 8Hz), 8.82 (1H, d, J = 5Hz), 10.39 (1H, bs). $^{m}/_{z}$ (API^{+}): 215 (MH^{+}).

Description 3 (E)-N-Quinolin-4-yl acrylamide (D3)

Quinoline-4-carboxylic acid (2.00g), diphenylphosphoryl azide (3.18g) and triethylamine (1.17g) were combined in 1,2-dichloroethane (50ml) and stirred for 16h. The mixture was warmed to reflux for 1h, cooled, a solution of acrylic acid (0.83g) in 1,2-dichloroethane (5ml) added and the mixture boiled for a further 3h. Solvent was removed at reduced pressure, the residue dissolved in dichloromethane and washed with water and saturated sodium chloride solution. The organic phase was dried ($MgSO_4$) and solvent removed at reduced pressure. The residue was triturated with ethyl acetate to give the title compound (0.52g). $^{m}/_{z}$ (API^{+}): 199 (MH^{+}).

Description 4 2-[(2,4-Difluorophenylamino)methylene]malonic acid diethyl ester (D4)

2,4-Difluoroaniline (12.2ml) and diethyl ethoxymethylenemalonate (24.3ml) were heated at 100°C under argon for 16h. The title compound was afforded as a beige solid (36.1g) following removal of the ethanol formed under reduced pressure then drying at 45°C *in vacuo*. ^{1}H NMR ($CDCl_3$) δ: 1.36 (6H, m), 4.28 (4H, m), 6.90 (2H, m), 7.30 (1H, m), 8.43 (1H, d, J = 13Hz), 11.30 (1H, d, J = 13Hz).

Description 5 6,8-Difluoro-4-hydroxyquinoline-3-carboxylic acid ethyl ester (D5)

D4 (15.0g) was heated at reflux in Dowtherm A (200ml) for 11h. The cooled reaction mixture was poured into hexane (250ml) and the preciptated solid was collected by filtration. Washing with hexane then drying at 45°C *in vacuo* afforded the title compound as a beige solid (7.30g). ^{1}H NMR δ: 1.42 (3H, t, J = 7Hz), 4.36 (2H, d, J = 7Hz), 7.78 (1H, m), 7.98 (1H, m), 8.53 (1H, s), 12.78 (1H, s).

Description 6 6,8-Difluoro-4-hydroxyquinoline-3-carboxylic acid (D6)

A solution of D5 (7.5g) and KOH (3.35g) in water/ethanol (25ml/250ml) was heated at reflux for 16h. After cooling the ethanol was removed at reduced pressure and the residue was acidified with HCl (2M). The preciptated solid was collected by filtration,

washing with water. The title compound was afforded as a white solid (6.2 g) after drying at 45°C *in vacuo*. ^{1}H NMR δ: 7.80 (1H, m), 8.06 (1H, m), 8.66 (1H, s), 13.76 (1H, bs), 14.75 (1H, bs).

Description 7 6,8-Difluoroquinolin-4-ol (D7)

D6 (6.0g) was heated at reflux in Dowtherm A for 3h. The cooled reaction mixture was poured into hexane (250ml). The precipitated solid was collected by filtration and washed with hexane to afford the title compound as a beige solid (4.2g). ^{1}H NMR δ: 6.10 (1H, d, J = 7Hz), 7.60 (1H, m), 7.75 (1H, m), 7.88 (1H, m), 12.03 (1H, bs).

Description 8 4-Chloro-6,8-difluoroquinoline (D8)

D7 (3.9g) was heated at reflux in phosphorus oxychloride (50ml), under argon for 4.5h. After cooling the excess phosphorus oxychloride was removed at reduced pressure and the residue partitioned between water and ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organics were washed with saturated aqueous sodium bicarbonate solution, dried (Na_2SO_4) and the solvent removed at reduced pressure to afford the title compound as a beige solid (4.0g). ^{1}H NMR ($CDCl_3$) δ: 7.32 (1H, m), 7.61 (1H, d, J = 5Hz), 7.70 (1H, m), 8.80 (1H, d, J = 5Hz).

Description 9 4-Amino-6,8-difluoroquinoline (D9)

A solution of D8 (3.8g) in pyridine (100ml) was treated with n-propylamine hydrochloride (9.1g) and the mixture heated at reflux for 16h. After cooling the pyridine was removed at reduced pressure and the residue partitioned between ethyl acetate and aqueous sodium hydroxide (10%). The aqueous phase was re-extracted with ethyl acetate and the combined organics were washed further with base. The organic phase was dried (Na_2SO_4) and the solvent removed at reduced pressure. The product was suspended in aqueous sodium hydroxide (10%) and extracted into ethyl acetate as above. The resulting residue was triturated with diethyl ether then chromatographed (silica gel, ethyl acetate) to afford the title compound as a brown solid (1.1g). ^{1}H NMR δ: 6.63 (1H, d, J = 5Hz), 6.93 (2H, bs), 7.54 (1H, m), 7.84 (1H, m), 8.32 (1H, d, J = 5Hz).

Description 10 4-Chloro-6,8-difluoro-2-methylquinoline (D10)

The title compound was prepared as a pale orange solid (3.0 g) by treating 6,8-difluoro-2-methylquinolin-4-ol (3.5g) with phosphorus oxychloride (40ml) as described for D8. ^{1}H NMR δ: 2.59 (3H, s), 7.70 (1H, m), 7.85 (2H, m).

Description 11 4-Azido-6,8-difluoro-2-methylquinoline (D11)

A solution of D10 (1.07g) in DMF (15 ml) was treated with sodium azide (0.65g) and the mixture stirred for 16h at room temperature then heated at 80°C for 20h. The cooled reaction mixture was poured onto ice/water and the product extracted into dichloromethane. The organic phase was dried (Na_2SO_4) and the solvent removed at reduced pressure. The residue was chromatographed (silica gel, 0-65 % ethyl acetate-

hexane) to afford the title compound as an off-white solid. (0.79g). ^{1}H NMR δ: 2.67 (3H, s), 7.46 (1H, m), 7.54 (1H, s), 7.75 (1H, m).

Description 12 4-Amino-6,8-difluoro-2-methylquinoline (D12)

A solution of D11 (0.22g) in methanol (15 ml) was treated with a pellet of sodium borohydride (approx. 0.40g) and the mixture stirred at room temperature for 1h. The methanol was removed at reduced pressure and the residue partitioned between ethyl acetate and water. The aqueous phase was re-extracted with ethyl acetate, the combined organics dried (Na_2SO_4) and the solvent removed at reduced pressure to afford the title compound as a white solid (0.16g). ^{1}H NMR δ: 2.42 (3H, s), 6.51 (1H, s), 6.79 (2H, bs), 7.48 (1H, m), 7.76 (1H, m).

Description 13 (E)-3-(Indol-7-yl)acrylic acid ethyl ester (D13)

7-Bromoindole (1.0g, Papparlado *et al*, *Gazz. Chim. Ital.*, 1958, **88**, 1147) was treated with acetonitrile (1.0ml), triethylamine (1.3ml), ethyl acrylate (1.0ml), phosphine (0.19g) and palladium(II)acetate (0.07g). The mixture was heated at 140°C for 1h under argon. A further portion of ethyl acrylate (0.40ml) was added and the mixture heated for a further 1h. After cooling the reaction mixture was partitioned between dichloromethane and water. After washing with water then saturated aqueous sodium chloride solution the organic phase was dried (Na_2SO_4) and the solvent removed at reduced pressure. Chromatography (silica gel, 25% diethyl ether-hexane) afforded the title compound (0.89g). $^m/_z$ (API$^+$): 170 (M-OEt).

Description 14 (E)-3-(Indol-7-yl)acrylic acid (D14)

A suspension of of D13 (0.84g) in water (100ml) was treated with sodium hydroxide solution (2M, 3.9ml). The mixture was heated for 1h at reflux. The cooled reaction mixture was extracted with ethyl acetate. The aqueous phase was acidified with HCl (5M), the precipitated solid collected by filtration and dried in vacuo to afford the title compound (0.62g). $^m/_z$ (API$^+$): 188(MH$^+$).

Description 15 4-Chloro[1,5]naphthyridine (D15)

4-Hydroxy[1,5]naphthyridine-3-carboxylic acid (14.00g, Adams *et al*, *J. Amer. Chem. Soc.*, 1946, **68**, 1317) in quinoline (150ml) was heated at reflux for 1h. The reaction mixture was cooled to room temperature then poured onto diethyl ether (500ml). The precipitated crude 4-hydroxy[1,5]naphthyridine was collected by filtration, washed with diethyl ether (4x300ml) and dried *in vacuo*. A sample of the solid (5.00g) was heated in phosphorus oxychloride (100ml) at 115°C under argon for 1h. The reaction mixture was cooled to room temperature and the resulting black oil treated with crushed ice with ice-salt bath cooling. The mixture was basified with .880 ammonia and then filtered through kieselguhr, washing with ethyl acetate. The organic phase of the filtrate was separated and the aqueous residues washed with ethyl acetate. The combined organics were washed with saturated aqueous sodium chloride and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the title compound as a waxy yellow solid (1.90g). ^{1}H NMR

($CDCl_3$) δ: 7.74 (2H, m), 8.46 (1H, dd, J = 2+9Hz), 8.87 (1H, d, J = 5Hz), 9.11 (1H, dd, J = 2+4Hz). $m/_z$ (API^+): 165, 167 (MH^+).

Description 16 4-Amino[1,5]naphthyridine (D16)

A solution of D15 (1.90g) in pyridine (80ml) was treated with n-propylamine hydrochloride (5.59g) and the mixture heated at reflux under argon for 5h. The reaction mixture was cooled and the pyridine removed under reduced pressure. The residue was treated with aqueous sodium hydroxide (10%) and the resulting solution extracted with diethyl ether. The combined organics were dried (Na_2SO_4) and the solvent removed under reduced pressure to give a sticky solid. Trituration with pentane afforded the title compound as a dark yellow solid (1.39g). ^1H NMR ($CDCl_3$) δ: 5.54 (2H, bs), 6.74 (1H, d, J = 5Hz), 7.58 (1H, dd, J = 4+8Hz), 8.25 (1H, dd, J = 2+8Hz), 8.53 (1H, d, J = 5Hz), 8.75 (1H, dd, J = 2 + 4Hz). $m/_z$ (API^+): 146 (MH^+).

Description 17 Trifluoromethanesulfonic acid 2-methyl[1,5]naphthyridin-4-yl ester (D17)

A suspension of 4-hydroxy-2-methyl[1,5]naphthyridine contaminated with 4-hydroxy-2-methyl[1,7]naphthyridine (1.0g, Walvaren *et al*, *J. Royal Netherlands Chem. Soc.*, 1976, **95**, 220) in dichloromethane (45ml) was treated sequentially with 2,6-lutidine (1.2ml), 4-N,N-dimethylaminopyridine (0.075g) and trifluoromethanesulfonic anhydride (1.2ml). After the final addition was complete the mixture was stirred for 0.5h, the mixture washed with saturated aqueous ammonium chloride, dried (Na_2SO_4) and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0-20% ethyl acetate in pentane) to afford the title compound as a colourless solid (0.588g). ^1H NMR ($CDCl_3$) : 2.84 (3H, s), 7.42 (1H, s), 7.73 (1H, dd), 8.37 (1H, dd), 9.04 (1H, m).

Description 18 4-Amino-2-methyl-[1,5]naphthyridine (D18)

D17 (2.2g) and n-propylamine hydrochloride (2.34g) were combined in pyridine (75ml) and the mixture heated at reflux for 8h. The solvent was removed at reduced pressure, the residue dissolved in aqueous sodium hydroxide (2M) and extracted with diethyl ether (3x) and dichloromethane (2x). The combined organic phase was dried and solvent removed at reduced pressure. The residue was triturated with pentane to give the title compound (1.32g) as a pale orange solid. ^1H NMR ($CDCl_3$) : 2.60 (3H, s), 5.44 (2H, bs), 6.66 (1H, s), 7.54 (1H, dd), 8.17 (1H, dd), 8.67 (1H, m).

Example 1 (E)-3-Benzo[1,3]dioxol-4-yl-N-quinolin-4-yl acrylamide

Quinoline-4-carboxylic acid (0.25g) in toluene (5ml) was treated with diphenylphosphoryl azide (0.3ml) and triethylamine (0.2ml). The reaction mixture was stirred at room temperature for 16h, boiled for 1h, 3-benzo[1,3]diox-4-yl acrylic acid (0.28g) (Nichols *et al*, *J. Med. Chem.*, 1990, **33**, 703) added and heating continued for 4h. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, 20% acetone-petroleum ether). Appropriate fractions were combined, solvent removed at reduced pressure and the residue re-chromatographed (silica gel, 5% methanol-diethyl

ether) to give the title compound (0.11g). ^{1}H NMR δ: 6.22 (2H, s), 6.93 - 7.04 (2H, m), 7.13 (1H, dd), 7.39 (1H, d, J = 16Hz), 7.62 - 7.68 (2H, m), 7.80 (1H, dt), 8.04 (1H, d), 8.27 (1H, d, J = 5Hz), 8.45 (1H, d), 8.83 (1H, d), 10.49 (1H, s). $^m/_z$ (API$^+$): 319 (MH$^+$).

Example 2 (E)-3-[2-(Furan-2-yl)phenyl]-N-quinolin-4-yl acrylamide

The title compound (0.11g) was prepared from quinoline-4-carboxylic acid (0.25g) and D2 (0.31g) according to the method of Example 1. ^{1}H NMR δ: ($CDCl_3$) 6.55 (1H, m), 6.65 (1H, d, J = 15Hz), 7.35 (1H, t, J = 8Hz), 7.489 (1H, t, J = 8Hz), 7.58 - 7.78 (m, 5H), 7.91 (1H, d, J = 8Hz), 8.15 (2H, m), 8.31 (1H, d, J = 15Hz), 8.44 (1H, d, J = 5Hz), 8.89 (1H, d, J = 5Hz). $^m/_z$ (API$^+$): 341 (MH$^+$).

Example 3 (E)-3-(3,4-Dihydro-2*H*-benzo[b][1,4]dioxepin-6-yl)-N-quinolin-4-yl acrylamide

The title compound (0.22g) was prepared from quinoline-4-carboxylic acid (0.17g) and 3-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-6-yl) acrylic acid (0.22g) (WO98/25606) according to the method of Example 1. ^{1}H NMR δ: 2.18 (2H, m), 4.18 (2H, t, J = 5Hz), 4.28 (2H, t, J = 5Hz), 7.06 (2H, m), 7.30 (1H, d, J = 16Hz), 7.37 (1H, m), 7.67 (1H, t), 7.79 (1H, t), 7.95 (1H, d, J = 16Hz), 8.04 (1H, d), 8.29 (1H, d, J = 5Hz), 8.46 (1H, d), 8.87 (1H, d), 10.37 (1H, s). $^m/_z$ (API$^+$): 347 (MH$^+$).

Example 4 (E)-3-(Indol-7-yl)-N-quinolin-4-yl acrylamide

The title compound (0.19g) was prepared from quinoline-4-carboxylic acid (0.17g) and D14 according to the method of Example 1. ^{1}H NMR δ: 6.54 (1H, m), 7.13 (1H, t, J = 8Hz), 7.40 (1H, d, J = 16Hz), 7.44 (1H, m), 7.54 (1H, d), 7.68 (2H, m), 7.82 (1H, t), 8.05 (1H, d), 8.29 (1H, d, J = 16Hz), 8.36 (1H, d, J = 5Hz), 8.51 (1H, d), 8.87 (1H, d), 10.36 (1H, s), 11.65 (1H, bs). $^m/_z$ (API$^+$): 314 (MH$^+$).

Example 5 (E)-3-(Thien-2-yl)-N-quinolin-4-yl acrylamide hydrochloride

The title compound was prepared from quinoline-4-carboxylic acid (0.50g) and (E)-3-(thien-2-yl)acrylic acid (0.43g) according to the method of Example 1.
^{1}H NMR δ: ($CDCl_3$) 6.54 (1H, d, J = 15Hz), 7.08 (1H, t, J = 1Hz), 7.29 (1H, d), 7.39 (1H, d, J = 5Hz), 7.60 (1H, t), 7.73 (1H, dt, J = 1+7Hz), 7.92 (2H, m), 8.13 (1H, d, J = 8Hz), 8.20 (1H, s), 8.39 (1H, d, J = 5Hz), 8.87 (1H, d, J = 5Hz). $^m/_z$ (API$^+$): 281 (MH$^+$).

Example 6 (E)-3-(Thien-3-yl)-N-quinolin-4-yl acrylamide hydrochloride

The title compound was prepared from quinoline-4-carboxylic acid (0.50g) and (E)-3-(thien-3-yl)acrylic acid (0.43g) according to the method of Example 1. ^{1}H NMR δ: ($CDCl_3$) 6.58 (1H, d, J = 15Hz), 7.26-7.37 (2H, m), 7.54-7.60 (2H, m), 7.73 (1H, t, J = 7Hz), 7.83 (1H, d, J = 15Hz), 7.94 (1H, d, J = 8Hz), 8.14 (1H, d, J = 8Hz), 8.23 (1H, s), 8.38 (1H, d, J = 5Hz), 8.87 (1H, d, J = 5Hz). $^m/_z$ (API$^+$): 281 (MH$^+$).

Example 7 (E)-3-Benzo[1,3]dioxol-4-yl-N-(8-fluoroquinolin-4-yl)acrylamide

A mixture of (E)-3-benzo[1,3]diox-4-yl acrylic acid (0.119g, Nichols *et al, J. Med. Chem.*, 1990, **33**, 703), 8-fluoro-4-aminoquinoline (0.100g) (WO93/04580), di-isopropylethylamine (0.080g) and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (0.235g) in dimethylformamide was stirred at room temperature for 16h. Solvent was removed at reduced pressure and the residual material triturated with water to give a yellow solid. The solid was column chromatographed (silica gel, ethyl acetate:hexane mixtures) to give the title compound (0.035 g). ^{1}H NMR δ: 6.23 (2H, s), 6.89-7.04 (2H, m), 7.13 (1H, dd, J = 1+8Hz), 7.39 (1H, d, J = 16Hz), 7.59-7.69 (3H, m), 8.29 (1H, m), 8.39 (1H, d, J = 5Hz), 8.88 (1H, d, J = 5.1Hz), 10.56 (1H, bs). $^m/_z$ (API$^+$): 337 (MH$^+$).

Example 8 (E)-3-(4-Methoxyphenyl)-N-quinolin-4-yl acrylamide

(E)-3-(4-Methoxyphenyl)acrylic acid (0.178g) was suspended in dichloromethane (20ml) and treated in turn with dimethylformamide (1 drop) and oxalyl chloride (0.262ml). After stirring for 1h solvent was removed at reduced pressure and the residue co-evaporated with toluene at reduced pressure. The formed acid chloride and 4-aminoquinoline (0.144g) were combined in pyridine and the mixture heated at 100°C for 16h. Solvent was removed at reduced pressure and the residue partitioned between dichloromethane and sodium hydroxide (2M). The organic phase was washed with brine, dried and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, ethyl acetate:hexane mixtures) to afford the title compound (0.16 g) as a colourless solid. ^{1}H NMR δ: ($CDCl_3$) 3.86 (3H, s), 6.59 (1H, d, J = 16Hz), 6.93 (2H, d, J = 9Hz), 7.54 (2H, d, J = 9Hz), 7.60 (1H, dt, J = 1+8Hz), 7.75 (1H, dt, J = 1+7Hz), 7.83 (1H, d, J = 15Hz), 7.92 (1H, d, J = 8Hz), 8.07 (1H, s), 8.15 (1H, d, J = 8Hz), 8.42 (1H, d, J = 5Hz), 8.88 (1H, d, J = 5Hz). $^m/_z$ (API$^+$): 305 (MH$^+$).

Example 9 (E)-3-(3-Methoxyphenyl)-N-quinolin-4-yl acrylamide

Quinoline-4-carboxylic acid (0.50g) and diphenylphosphoryl azide (0.77g) were combined in dichloroethane (10ml) containing triethylamine (0.39ml) and stirred at room temperature for 16h. The mixture was boiled for 0.5h (E)-3-(3-methoxyphenyl)acrylic acid (0.49g) in 1,2-dichloroethane (3ml) was added to the cooled solution and the reaction refluxed for 4h. Solvent was removed at reduced pressure, the residue dissolved in dichloromethane and washed with saturated sodium hydrogen carbonate and brine. Solvent was removed at reduced pressure and the residue column chromatographed (silica gel, dichloromethane: methanol:ammonia mixtures) to give the title compound (0.25g) as a colourless solid. ^{1}H NMR δ: ($CDCl_3$) 3.84 (3H, s), 6.73 (1H, d, J = 15Hz), 6.96 (1H, dd, J = 2+8Hz), 7.07 (1H, m), 7.15 (1H, J=8Hz), 7.32 (1H, t, J = 8Hz), 7.58 (1H, dt, J = 1+7Hz), 7.73 (1H, dt, J = 1+8Hz), 7.83 (1H, d, J = 15Hz), 7.93 (1H, d, J = 8Hz), 8.14 (1H, d, J = 8Hz), 8.22 (1H, s), 8.40 (1H, d, J = 5Hz), 8.88 (1H, d, J = 5Hz). $^m/_z$ (API$^+$): 305 (MH$^+$).

Example 10 (E)-3-(2-Methoxyphenyl)-N-quinolin-4-yl acrylamide

The title compound (0.26g) was prepared from 4-quinolinecarboxylic acid (0.50g) and (E)-3-(2-methoxyphenyl)acrylic acid (0.50g) according to the method of Example 9.

^{1}H NMR δ: ($CDCl_3$) 3.93 (3H, s), 6.87 (1H, d, J = 16Hz), 6.94-7.02 (2H, m), 7.39 (1H, dt), 7.43-7.63 (2H, m), 7.74 (1H, dt), 7.93 (1H, d), 8.08-8.15 (3H, m), 8.43 (1H, d), 8.89 (1H, d). $m/_z$ (API^+): 305 (MH^+).

Example 11 (E)-3-(4-Chlorophenyl)-N-quinolin-4-ylacryl amide hydrochloride

The title compound (0.088 g) was prepared from 4-quinolinecarboxylic acid (0.500g) and (E)-3-(4-chlorophenyl)acrylic acid (0.509g) according to the method of Example 9. The product was converted to the hydrochloride. ^{1}H NMR δ: ($CDCl_3$) 6.70 (1H, d, J = 17Hz), 7.44 (2H, d, J = 9Hz), 7.50 (2H, d, J = 8Hz), 7.60 (1H, dt, J = 1+8Hz), 7.75 (1H, dt, J = 1+ 8Hz), 7.81 (1H, d, J = 17Hz), 7.92 (1H, d, J = 8Hz), 8.15 (2H, m), 8.39 (1H, d, J = 5Hz), 8.89 (1H, d, J = 5Hz). $m/_z$ (API^+): 309, 311 (MH^+).

Example 12 (E)-3-Phenyl-N-quinolin-4-yl acrylamide hydrochloride

The title compound (0.169g) was prepared from quinoline-4-carboxylic acid (0.500g) and (E)-3-phenylacrylic acid (0.413g) according to the method of Example 9. The product was converted to the hydrochloride. ^{1}H NMR δ: 7.31 (1H, d, J = 16Hz), 7.47-7.54 (3H, m), 7.65-7.72 (3H, m), 7.80 (1H, dt, J = 1+7Hz), 8.03 (1H, d, J = 8Hz), 8.31 (1H, d, J = 5Hz), 8.46 (1H, d, J = 8Hz), 8.83 (1H, d, J = 5Hz), 10.39 (1H, bs). $m/_z$ (API^+): 275 (MH^+).

Example 13 (E)-3-(3-Methylphenyl)-N-quinolin-4-yl acrylamide hydrochloride

The title compound (0.156g) was prepared from quinoline-4-carboxylic acid (0.500g) and 3-(3-methylphenyl)acrylic acid (0.452g) according to the method of Example 9. The product was converted to the hydrochloride. ^{1}H NMR δ: 2.31 (3H, s), 7.15-7.35 (3H, m), 7.43 (2H, m), 7.59-7.65 (2H, m), 7.74 (1H, t, J = 7Hz), 7.96 (1H, d, J = 8Hz), 8.25 (1H, d, J = 5Hz), 8.39 (1H, d, J = 8Hz), 8.76 (1H, d, J = 5Hz), 10.29 (1H, bs). $m/_z$ (API^+): 289 (MH^+).

Example 14 (E)-3-(3-N,N-Dimethylaminophenyl)-N-quinolin-4-yl acrylamide

A mixture of D3 (0.32 g), 3-bromo-N,N-dimethylaniline (0.32g), palladium (II) acetate (0.02g), tris(o-tolyl)phosphine (0.05g) and triethylamine (0.24g) in acetonitrile (7ml) was boiled for 5h. The mixture was cooled to room temperature, diluted with dichloromethane and washed with water and brine. The organic phase was dried ($MgSO_4$) and solvent removed at reduced pressure. The residue was triturated with dichloromethane to give the title compound (0.283g) as a pale green solid. ^{1}H NMR δ: 2.97 (6H, s), 6.81 (1H, dd, J = 2+8Hz), 6.98-7.01 (2H, m), 7.23-7.32 (2H, m), 7.64-7.70 (2H, m), 7.80 (1H, dt, J = 1+7Hz), 8.02 (1H, d, J = 8Hz), 8.31 (1H, d, J = 5Hz), 8.45 (1H, d, J = 8Hz), 8.82 (1H, d, J = 5Hz), 10.34 (1H, bs). $m/_z$ (API^+): 318 (MH^+).

Example 15 (E)-3-(2-N,N-Dimethylaminophenyl)-N-quinolin-4-yl acrylamide

The title compound (0.18g) was prepared from D3 (0.20g) and 2-bromo-N,N-dimethylaniline (0.20g) according to the method of Example 14. Product was isolated by

column chromatography. ^{1}H NMR δ: ($CDCl_3$). 2.67 (6H, s), 6.81-6.87 (2H, m), 7.00 (1H, d, J = 8Hz), 7.27 (1H, t, J = 7Hz), 7.35-7.46 (2H, m), 7.64 (1H, t, J = 7Hz), 8.07 (2H, d, J = 9Hz), 8.18 (1H, d, J = 16Hz), 8.38 (1H, d, J = 5Hz), 8.79 (1H, d, J = 5Hz), 9.08 (1H, s). $^m/_z$ (API^+): 318 (MH^+).

Example 16 (E)-3-Benzo[1,3]dioxol-4-yl-N-(2-methylquinolin-4-yl) acrylamide

A mixture of 2-methyl-4-aminoquinoline (0.08g), 3-benzo[1,3]diox-4-yl acrylic acid (0.096g, Nichols *et al, J. Med. Chem.*, 1990, **33**, 703), di-isopropylethylamine (0.09ml) and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.19g) were combined in dimethylformamide (2ml) and stirred at room temperature for 16h. NaOH (2M, 2ml) and water were added and the precipitated solid separated by filtration and washed thoroughly with water to give the title compound (0.057g). ^{1}H NMR δ: 2.64 (3H, s), 6.22 (2H, s), 6.90-7.03 (2H, m), 7.12 (1H, d, J = 8Hz), 7.37 (1H, d, J = 16Hz), 7.57 (1H, t, J = 7Hz), 7.63 (1H, d, J = 16Hz), 7.73 (1H, t, J = 7.3Hz), 7.91 (1H, d, J = 8Hz), 8.17 (1H, s), 8.37 (1H, d, J = 8Hz), 10.44 (1H, s). $^m/_z$ (API^+): 333 (MH^+).

Example 17 (E)-3-Benzo[1,3]dioxol-4-yl-N-(6,8-difluoroquinolin-4-yl) acrylamide

A solution of (E)-3-benzo[1,3]dioxol-4-yl acrylic acid (0.106g, Nichols *et al, J. Med. Chem.*, 1990, **33**, 703) in DMF (12ml) was treated with di-isopropylethylamine (0.087ml) then O-(7-azabenzotriazol-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.190g). D9 (0.090g) was added and the mixture stirred for 1h at room temperature under argon. The reaction mixture was heated at 65°C for 40h. After cooling the reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic phase was separated and washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried (Na_2SO_4) and the solvent removed at reduced pressure. Chromatography (silica gel, 20-100% ethyl acetate-hexane) afforded the title compound as an orange solid (6mg). ^{1}H NMR δ: 6.22 (2H, s), 6.98 (2H, m), 7.13 (1H, dd, J = 1+8Hz), 7.35 (1H, m), 7.73 (1H, d, J = 22Hz), 7.78 (1H, m), 8.20 (1H, m), 8.45 (1H, d, J = 7Hz), 8.84 (1H, d, J = 7Hz), 10.40 (1H, s). $^m/_z$ (API^+): 355 (MH^+).

Example 18 (E)-3-Benzo[1,3]dioxol-4-yl-N-(6,8-difluoro-2-methylquinolin-4-yl) acrylamide

A solution of (E)-3-benzo[1,3]dioxol-4-yl acrylic acid (0.048g, Nichols *et al, J. Med. Chem.*, 1990, **33**, 703) in DMF (4ml) was treated with di-isopropylethylamine (0.106ml) then tetramethylfluoroformamidinium hexafluorophosphate (TFFH) (0.079g). D12 (0.049g) was added and the mixture stirred at 100°C for 24h. The reaction mixture was cooled then diluted with water. The precipitated solid was collected by filtration, washing with water then diethyl ether. Drying at 40°C under reduced pressure afforded the title compound as an off-white solid. ^{1}H NMR δ: 2.50 (3H, s), 6.07 (2H, s), 6.80 (2H, m), 6.97 (1H, d, J = 7Hz), 7.19 (1H, d, J = 16Hz), 7.48 (1H, d, J = 16Hz), 7.58 (1H, m), 7.97(1H, d, J = 11Hz), 8.18 (1H, s), 10.18 (1H, s). $^m/_z$ (API^+): 369 (MH^+).

Example 19 (E)-N-(6,8-Difluoro-2-methylquinolin-4-yl)-3-(2-methoxyphenyl)acrylamide

D12 (0.194g) was added to a stirring solution of (E)-3-(2-methoxyphenyl)acryloyl chloride (0.137g) in pyridine (2.5ml). The reaction mixture was stirred at 100°C for 15h. After cooling the solvent was removed at reduced pressure and the residue washed with water, diethyl ether then dichloromethane to afford the title compound as a beige solid (0.236g). ^{1}H NMR δ: 2.65 (3H, s), 3.92 (3H, s), 7.1 (2H, m), 7.28 (1H, d, J = 16Hz), 7.45 (1H, t, J = 8Hz), 7.70 (2H, m), 7.94 (1H, d, J = 16Hz), 8.10 (1H, d, J = 11Hz), 8.35 (1H, s), 10.20 (1H, s). $^m/_z$ (API$^+$): 355 (MH$^+$).

Example 20 (E)-3-(2-Methoxyphenyl)-N-[1,5]naphthyridin-4-yl acrylamides

(E)-3-(2-Methoxyphenyl)acryloyl chloride (0.108g) in dichloromethane (3ml) was added to a stirring mixture of D16 (0.080g) and 4-N,N-dimethylaminopyridine (0.065g) in dichloromethane (8ml). After stirring at room temperature under argon for 16h the reaction mixture was diluted with dichloromethane (50ml) and washed with water then saturated aqueous sodium chloride. The organic phase was dried (Na_2SO_4) and the solvent removed at reduced pressure to afford a yellow solid. Chromatography (silica gel, 20-100% ethyl acetate in pentane) followed by trituration with diethyl ether afforded the title compound as a pale yellow solid (0.098 g). ^{1}H NMR δ: 3.85 (3H, s), 7.00 (2H, m), 7.40 (1H, m), 7.55 (1H, d, J = 16Hz), 7.67 (1H, d, J = 8Hz), 8.00 (2H, m), 8.53 (1H, d, J = 9Hz), 8.82 (1H, d, J = 5Hz), 9.02 (1H, d, J = 5Hz), 9.03 (1H, m), 11.17 (1H, s). $^m/_z$ (API$^+$): 306 (MH$^+$).

Example 21 (E)-3-Benzo[1,3]dioxol-4-yl-N-[1,5]naphthyridin-4-yl acrylamide

A solution of (E)-3-benzo[1,3]dioxol-4-yl acrylic acid (0.096g, Nichols *et al, J. Med. Chem.*, 1990, **33**, 703) in DMF (1ml) was treated with di-isopropylethylamine (0.087ml) then O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (0.190g). D16 (0.073g) in DMF (1ml) was added and the mixture stirred for 72h at room temperature under argon. The reaction mixture was added drop-wise to saturated aqueous potassium carbonate and the precipitated solid collected by filtration. Chromatography (silica gel, 20-100 % ethyl acetate in pentane) afforded the title compound (0.040g). ^{1}H NMR δ: 6.20 (2H, s), 6.98 (2H, m), 7.19 (1H, dd, J = 1+8Hz), 7.55 (1H, d, J = 16Hz), 7.67 (1H, d, J = 16Hz), 7.89 (1H, dd, J = 4+9Hz), 8.45 (1H, dd, J = 2+9Hz), 8.67 (1H, d, J = 5Hz), 8.90 (1H, d, J = 5Hz), 9.03 (1H, dd, J = 2+4Hz), 10.86 (1H, s). $^m/_z$ (API$^+$): 320 (MH$^+$).

Example 22 (E)-3-Benzo[1,3]dioxol-4-yl-N-(2-methyl-[1,5]naphthyridin-4-yl)-acrylamide

A solution of (E)-3-benzo[1,3]dioxol-4-yl acrylic acid (0.576g, Nichols *et al, J. Med. Chem.*, 1990, **33**, 703) in DMF (3ml) was treated with di-isopropylethylamine (0.053ml) in DMF (0.3ml) then O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.114g) in DMF (0.6ml). A solution of D18 (0.040g) in DMF (1ml)

was added and the mixture was shaken for 24 h at room temperature. The reaction mixture was treated with aqueous sodium hydroxide solution (2M, 8ml) then cooled. The precipitated solid was collected by filtration, washed with water and diethyl ether then dried *in vacuo* to give the title compound as a solid (20mg). ^{1}H NMR δ: 2.85 (3H, s), 6.36 (2H, s), 7.12 (2H, m), 7.36 (1H, dd, J = 1+8Hz), 7.70 (1H, d, J = 16Hz), 7.82 (1H, d, J = 16Hz), 7.99 (1H, dd, J = 4+9 Hz), 8.50 (1H, dd, J = 1+8Hz), 8.75 (1H, s), 9.10 (1H, m), 10.91 (1H, s). $^m/_z$ (API$^+$): 334 (MH$^+$).

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

HEK293 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37°C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC_{50} values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC_{50} values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 90 min at 37°C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x 150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37°C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument and maintained at 37°C in humidified air. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against

compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, 1995, *TiPS*, 16, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

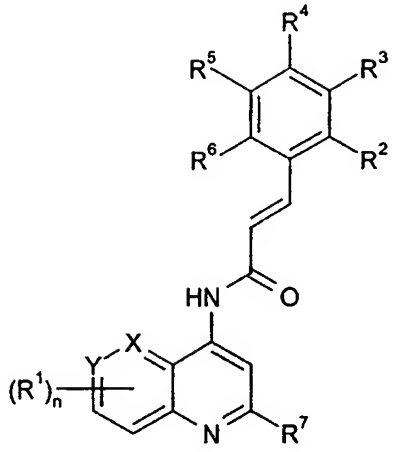
$K_b = IC_{50}/(1+([3/EC_{50}])$

where EC_{50} was the potency of human orexin-A determined in the assay (in nM terms) and IC_{50} is expressed in molar terms.

As an illustration of the activity of the compounds of formula (I), the compounds of Examples 1, 7, 17 and 18 had a pKb > 6.5 in this assay, and compounds of Examples 20-22 had a pKb > 6.

CLAIMS

1. A compound of formula (I):



(I)

in which:

X and Y are CH, or one of X and Y is N and the other is CH;

R^1 represents (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{1-6})alkoxy, any of which may be optionally substituted; halogen, R^8CO- or $NR^9R^{10}CO$-;

R^2, R^3, R^4, R^5 and R^6 independently represent (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxy or (C_{1-6})alkylthio, any of which may be optionally substituted; hydrogen, halogen, nitro, cyano, aryloxy, aryl(C_{1-6})alkyloxy, aryl(C_{1-6})alkyl, R^8CO-, R^8SO_2NH-, R^8SO_2O-, $R^8CON(R^{11})$-, NR^9R^{10}-, $NR^9R^{10}CO$-, -$COOR^9$, $R^{11}C(=NOR^8)$, heterocyclyl or heterocyclyl(C_{1-6})alkyl;

or an adjacent pair of R^2, R^3, R^4, R^5 and R^6 together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic ring;

R^7 is hydrogen, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{1-6})alkoxy or (C_{1-6})alkylthio, any of which may be optionally substituted; halogen, hydroxy, nitro, cyano, NR^9R^{10}-, $NR^9R^{10}CO$-, N_3, -$OCOR^9$ or $R^8CON(R^{11})$-;

R^8 is (C_{1-6})alkyl, (C_{2-6})alkenyl, heterocyclyl, heterocyclyl(C_{1-6})alkyl, aryl or aryl(C_{1-6})alkyl, any of which may be optionally substituted;

R^9 and R^{10} independently represent hydrogen, (C_{1-6})alkyl, (C_{2-6})alkenyl, heterocyclyl, heterocyclyl(C_{1-6})alkyl, aryl or aryl(C_{1-6})alkyl, any of which may be optionally substituted;

R^{11} is hydrogen or (C_{1-6})alkyl; and

when X and Y are both CH, n is 0, 1, 2, 3 or 4, and when X or Y is N, n is 0, 1, 2 or 3; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which R^7 is other than hydrogen.

3. A compound according to claim 1 or claim 2 in which:
either X or Y is N and n is 0 or 1; or X and Y are CH and n is 1 or 2.

4. A compound according to any one of the preceeding claims in which X is N and Y is CH.

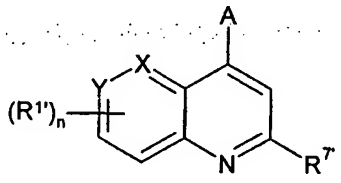
5. A compound according to any one of the preceding claims in which R^2 to R^6 independently represent hydrogen, halogen, (C_{1-6})alkoxy, (C_{1-6})alkylthio or NR^9R^{10}, and at least one of R^2 to R^6 is other than hydrogen; or an adjacent pair of R^2 to R^6 together with the carbon atoms to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring.

6. A compound according to any one of the preceding claims in which either R^5 or R^6, or R^4 and R^6 represent hydrogen.

7. A compound according to any one of claims 1 to 5 in which either R^2, R^2 and R^3, R^3 and R^4, or R^3 and R^5 are other than hydrogen.

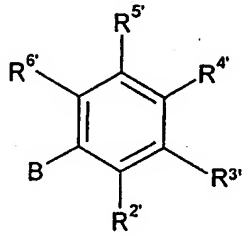
8. A process for the preparation of a compound of formula (I) as defined in any one of the preceding claims or a salt thereof which comprises:

a) coupling a compound of formula (II):



(II)

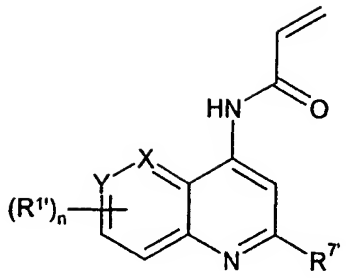
with a compound of formula (III):



(III)

where A and B are appropriate functional groups to form the –NHCOCH=CH- moiety when coupled; n, X and Y are as defined in formula (I); and $R^{1'}$ to $R^{7'}$ are R^1 to R^7 as defined in formula (I) or groups convertible thereto; or

b) coupling a compound of formula (IV):



(IV)

wherein n, X and Y are as defined in formula (I); and $R^{1'}$ and $R^{7'}$ are R^1 and R^7 as defined in formula (I) or groups convertible thereto; with a compound of formula (III) where B is a halogen or trifluoromethanesulfonate, in the presence of a palladium catalyst, a phosphine and a base; and

c) thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$ to $R^{7'}$ when other than R^1 to R^7 respectively to R^1 to R^7, and/or forming a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. The use of a compound of formula (I) as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01148

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 C07D401/12 C07D409/12 C07D471/04 C07D215/42
A61K31/4706 A61K31/4375 A61P25/00 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 58533 A (SMITHKLINE BEECHAM PLC, UK) 18 November 1999 (1999-11-18) cited in the application claims	1-10
P,A	WO 99 09024 A (SMITHKLINE BEECHAM PLC, UK) 25 February 1999 (1999-02-25) cited in the application claims	1-10
A	EP 0 849 361 A (SMITHKLINE BEECHAM CORP., USA;SMITHKLINE BEECHAM PLC) 24 June 1998 (1998-06-24) cited in the application the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 2000	05/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schmid, J-C

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. .tional Application No
PCT/EP 00/01148

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9958533 A	18-11-1999	AU 4037799 A	29-11-1999
WO 9909024 A	25-02-1999	AU 8741198 A	08-03-1999
EP 0849361 A	24-06-1998	CA 2218452 A	07-06-1998
		JP 10229887 A	02-09-1998
		US 6001963 A	14-12-1999